Patrick: An Introduction to Medicinal Chemistry 5e
Chapter 1

DRUGS & DRUG TARGETS
AN OVERVIEW
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1. Cell Structure

- Plasma membrane
- Cytoplasm
- Nucleus

Phospholipid bilayer
1. Cell Structure

Notes:

• Human, animal and plant cells are eukaryotic cells

• The nucleus contains the genetic blueprint for life (DNA)

• The fluid contents of the cell are known as the cytoplasm

• Structures within the cell are known as organelles

• Mitochondria are the source of energy production

• Ribosomes are the cell’s protein ‘factories’

• Rough endoplasmic reticulum is the location for protein synthesis
2. Cell Membrane

Exterior
High [Na$^+$]

Interior
High [K$^+$]

Phospholipid Bilayer

Proteins
2. Cell Membrane

Polar Head Group

Hydrophobic Tails

Polar Head Group

Hydrophobic Tails
2. Cell Membrane

Polar Head Group

Hydrophobic Tails

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2. Cell Membrane

**Notes:**

- The cell membrane is made up of a phospholipid bilayer

- The hydrophobic tails interact with each other by van der Waals interactions and are hidden from the aqueous media

- The polar head groups interact with water at the inner and outer surfaces of the membrane

- The cell membrane provides a hydrophobic barrier around the cell, preventing the passage of water and polar molecules

- Proteins are embedded in the cell membrane (ion channels, receptors, enzymes and transport proteins)
3. Drug targets

Lipids

Cell membrane lipids

Proteins

Receptors
Enzymes
Transport proteins
Structural proteins (tubulin)

Nucleic acids

DNA
RNA

Carbohydrates

Cell surface carbohydrates
Antigens and recognition molecules
3. Drug targets

Notes

• Drug targets are large molecules - macromolecules
• Drugs are generally much smaller than their targets
• Drugs interact with their targets by binding to binding sites
• Binding sites are typically hydrophobic hollows or clefts on the surface of macromolecules
• Binding interactions typically involve intermolecular bonds
• Most drugs are in equilibrium between being bound and unbound to their target
• Functional groups on the drug are involved in binding interactions and are called binding groups
• Specific regions within the binding site that are involved in binding interactions are called binding regions
3. Drug targets

Macromolecular target

Unbound drug

Induced fit

Bound drug

Drug

Binding site

Binding regions

Binding groups

Intermolecular bonds

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3. Drug targets

Notes

• Binding interactions usually result in an induced fit where the binding site changes shape to accommodate the drug

• The induced fit may also alter the overall shape of the drug target

• Important to the pharmacological effect of the drug
4. Intermolecular bonding forces

4.1 Electrostatic or ionic bonds

- Strongest of the intermolecular bonds (20-40 kJ mol\(^{-1}\))
- Takes place between groups of opposite charge
- The strength of the ionic interaction is inversely proportional to the distance between the two charged groups
- Stronger interactions occur in hydrophobic environments
- The strength of interaction drops off less rapidly with distance than with other forms of intermolecular interactions
- Ionic bonds are the most important initial interactions as a drug enters the binding site
4. Intermolecular bonding forces
4.2 Hydrogen bonds

- Vary in strength
- Weaker than electrostatic interactions but stronger than van der Waals interactions
- A hydrogen bond takes place between an electron-deficient hydrogen and an electron-rich heteroatom (N or O)
- The electron-deficient hydrogen is usually attached to a heteroatom (O or N)
- The electron-deficient hydrogen is called a hydrogen bond donor
- The electron-rich heteroatom is called a hydrogen bond acceptor
4. Intermolecular bonding forces
4.2 Hydrogen bonds

• The interaction involves orbitals and is directional

• Optimum orientation is where the X-H bond points directly to the lone pair on Y such that the angle between X, H and Y is $180^\circ$
4. Intermolecular bonding forces
4.2 Hydrogen bonds

• Examples of strong hydrogen bond acceptors
  - carboxylate ion, phosphate ion, tertiary amine

• Examples of moderate hydrogen bond acceptors
  - carboxylic acid, amide oxygen, ketone, ester, ether, alcohol

• Examples of poor hydrogen bond acceptors
  - sulfur, fluorine, chlorine, aromatic ring, amide nitrogen, aromatic amine

• Example of good hydrogen bond donors
  - aminium ions (HNR₃⁺)
4. Intermolecular bonding forces
4.3 Van der Waals interactions

- Very weak interactions (2-4 kJ mol\(^{-1}\))
- Occur between hydrophobic regions of the drug and the target
- Transient areas of high and low electron densities cause temporary dipoles
- Interactions drop off rapidly with distance
- Drug must be close to the binding region for interactions to occur
- The overall contribution of van der Waals interactions can be crucial to binding
4. Intermolecular bonding forces

4.4 Dipole-dipole interactions

- Can occur if the drug and the binding site have dipole moments
- Dipoles align with each other as the drug enters the binding site
- Dipole alignment orientates the molecule in the binding site
- Orientation is beneficial if other binding groups are positioned correctly with respect to the corresponding binding regions
- Orientation is detrimental if the binding groups are not positioned correctly
- The strength of the interaction decreases with distance more quickly than with electrostatic interactions, but less quickly than with van der Waals interactions
4. Intermolecular bonding forces
4.4 Dipole-dipole interactions
4. Intermolecular bonding forces

4.5 Ion-dipole interactions

- Occur where the charge on one molecule interacts with the dipole moment of another
- Stronger than a dipole-dipole interaction
- Strength of interaction falls off less rapidly with distance than for a dipole-dipole interaction
4. Intermolecular bonding forces

4.6 Induced dipole interactions

- Occur where the charge on one molecule induces a dipole on another
- Occur between a quaternary ammonium ion and an aromatic ring
5. Desolvation penalties

- Polar regions of a drug and its target are solvated prior to interaction
- Desolvation is necessary and requires energy
- The stabilisation energy gained by drug-target interactions must be greater than the energy penalty required for desolvation
6. Hydrophobic interactions

- Hydrophobic regions of a drug and its target are not solvated
- Water molecules interact with each other and form an ordered layer next to hydrophobic regions - negative entropy
- Interactions between the hydrophobic regions of a drug and its target ‘free up’ the ordered water molecules
- Results in an increase in entropy
- Beneficial to binding energy